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Applicant(s): Nikolic-Zugich	
Application No.: 09/719,494	
Filed: 12/13/2000	Group Art Unit: 1644
Title: Vaccination Strategy to Prevent and Treat Cancers	Examiner: M. DiBrino
Attorney Docket No.: MSK.P-042	

BRIEF FOR APPELLANT

This brief is filed in support of Applicants' Appeal from the final rejection mailed 3/31/2004. Consideration of the application and reversal of the rejections are respectfully urged.

Real Party in Interest

The real party in interest is Sloan-Kettering Institute for Cancer Research.

Related Appeals and Interferences

To Applicants' knowledge, there are no related Appeals or Interferences.

Status of Claims

Claims 1-16 are pending. Claims 5-8, 10 and 15 are withdrawn from consideration as drawn to a non-elected species. Claims 17-33 have been canceled.

Claim 14 is objected to, but has been indicated to be allowable. Claims 1-4, 9, 11-13, and 16 are the subject of this appeal.

Status of Amendments

All amendments have been entered.

Summary of Claimed Subject Matter

The present invention relate to a method for inducing a cellular response to a target peptide that is non-immunogenic in a mammalian subject, and that is expressed by tumor cells of a mammalian subject. (Specification, page 2, lines 15-18; Claim 1) A "cellular immune response" is a response that involves cytotoxic T lymphocytes (CTL), as opposed to merely a humoral, antibody response. (Page 3, lines 22-24). The method of the invention involves administration of a therapeutic antigen which is effective to induce the cellular response, even though the target peptide is not. (Page 5, lines 1-5) This therapeutic antigen comprises an immunogenic portion having an MHC-binding domain which binds to the major histocompatability complex (MHC) and an immune recognition domain which is recognized by T-cells (See, Page 4, lines 21-27). The therapeutic antigen is derived from the target peptide such that the MHC-binding portion binds to MHC with a greater affinity than the target peptide without material alteration of the immune-recognition portion, thereby inducing a therapeutically effective cellular immune response to the target peptide in the mammalian subject. (Page 2, lines 20-24, Page 6, lines 3-16) As explained on Page 4, line 30 et seq. "the term 'derived from' refers to peptides which have an amino acid sequence which is based at least in part on the structure of the naturally occurring non-immunogenic" target peptide.

Grounds of Rejection to be reviewed on Appeal

Claims 1, 2, 9, 11 and 12 stand rejected as anticipated under 35 USC § 102(b) by WO 95/29193, as evidenced by Overwijk et al.

Claims 1, 2, and 9 stand rejected as anticipated under 35 USC § 102(b) by Lipford et al.

Claims 1, 2, 9 and 16 stand rejected as anticipated under 35 USC § 102(a) by Huard et al, as evidenced by alleged admissions in the Applicants' specification.

Claims 1-4, 9, 11 and 12 stand rejected under 35 USC § 103(a) as obvious over WO 95/29193, in view of Anderson et al. and Yewdell et al.

Claims 1-4, 9 and 11 stand rejected under 35 USC § 103(a) as obvious over Lipford, in view of Anderson et al. and Yewdell et al.

Claims 1, 2, 9 and 16 stand rejected under 35 USC § 103(a) as obvious over Huard et al, in view of alleged admissions in the Applicants' specification.

Claims 1-4, 9 and 16 stand rejected under 35 USC § 103(a) as obvious over Huard et al, in view of alleged admissions in the Applicants' specification, and further in view of Anderson et al. and Yewdell et al.

Argument

The present invention addresses the problem of developing an immune response to a target peptide, that is expressed by tumor cells in an individual, where the target peptide does not itself stimulate an immune response. In general, this is observed where the protein is a "self-protein", i.e., a protein that the immune system of the individual does not recognize as foreign and which is therefore tolerated. Thus, the present invention provides a mechanism for convincing the immune system of a cancer patient to mount a defense against the tumor, thus providing a method both for treating existing disease, and for reducing the risk of disease recurrence.

The method of the invention accomplishes this result by using a modification of a target peptide as an immunogen. Modified or "heteroclitic" peptides based on naturally occurring peptides have been previously described in the art for vaccine uses. In each case, however, the starting peptide is itself immunogenic to some extent, and the purpose of the modification is to make it a better immunogen. In the present case, the starting peptide is one that is non-immunogenic. As discussed below, the art cited by the Examiner does not show conversion of non-immunogenic starting peptides into immunogens. The use of a non-immunogenic peptide as a starting point, however, has important consequences to the use of the therapeutic antigen in treatment of cancer. Thus, as explained in the specification on page 4, lines 10-20, the ability of an unmodified antigen to induce a CTL response is actually part of the reason why tolerance is developed. Non-immunogenic peptides "fail to induce tolerance, and the T cell repertoire reactive against them is intact and available for activation with immunogenic variants."

Claims 1, 2, 9, 11 and 12 are not anticipated by WO 95/29193

In order to establish anticipation, the Examiner must show that each and every element of the claimed invention is taught, either expressly or inherently, in a single prior art reference. The Examiner states that the WO95/29193 reference "teaches a method of inducing an immune response by administering heteroclitic peptides from tumor antigens, including gp100, altered to improve peptide MHC Class I (including HLA-A2.1) binding affinity and to render the peptide capable of inducing an immune response." Overwijk is cited to support a contention that gp100 is inherently weakly immunogenic, and that CTL with reactivity to gp100 have been detected in patients with metastatic melanoma. (Office Action of 3/31/2004, Page 3). Weakly immunogenic is not the same as "non-immunogenic", however, which is what is required in the pending claims. Thus, by the Examiner's own argument, the reference fails to meet the limitations of the present claims. Thus, there can be no anticipation and the rejection should be reversed.

Claims 1, 2, and 9 are not anticipated by Lipford et al.

Lipford et al. discloses heteroclitic peptides based on human papilloma virus tumor antigen E6. This is not a self-peptide, but a foreign viral peptide, and the Examiner has therefore correctly not included claim 12, in this rejection. The gist of the Examiner's argument is that Lipford discloses a peptide fragment of the E6 antigen which was non-immunogenic in mice, and the modification of this fragment to one that is immunogenic. Applicants respectfully submit that this teaching does not meet all of the limitations of claim 1, and therefore that neither claim 1 nor claims 2 and 9 which are dependent thereon are anticipated.

As a first matter, the target peptide, as set forth in the claim 1, is one which is non-immunogenic in a mammalian subject and that is expressed by tumor cells of the mammalian subject. Furthermore, the modified peptide is one that does induce a cellular immune response in this mammalian subject. There is no indication in the Lipford paper that the mammalian subject (a mouse) to which the antigens were administered is one in which the target peptide was expressed on tumor, or any other type of cells. Thus, the subject mammal in Lipford does not meet the limitations of the present claims. This is significant because if the target

peptide was expressed, particularly as the intact E6 antigen it is possible that either or both results would be different. For example, in the presence of a prior sensitization to E6, the initial peptide could have been immunogenic. On the other hand, prior sensitization to E6 could have created a tolerance in which case the modified peptide might not have been immunogenic either.

Furthermore, the present claims require induction of a "therapeutically effective" immune response against the target peptide. In the case of the Lipford paper, this would require a therapeutically effective response against human papilloma virus. The paper, however, only shows the ability *in vitro* to lyse cells expressing E6 using CTL generated by immunization with the modified peptide. The paper does not demonstrate that an *in vivo* response that is of any benefit in the treatment of human papilloma virus is obtained. Further, the conclusion of the paper is that in designing heteroclitic peptides those starting peptides of lesser activity should not be excluded from study, but there is no suggestion that the particular peptide made in the paper would have utility as a therapeutic.

Given these differences, the legal standard for anticipation is not met. This rejection should therefore be reversed.

Claims 1, 2, 9 and 16 are not anticipated by Huard et al.

The Huard paper describes a study on heteroclitic peptides to investigate the structural reasons for differential binding. The study looks at a peptide OVA-8 and fragments of herpes simplex virus. One of the peptides tested is SSIEFARL which is the therapeutic antigen recited in claim 16 for use when the target peptide is a Herpes simplex glycoprotein B peptide. However, no tests are reported in which a mammalian subject have tumor cells expressing HSV was treated with the peptides and no teaching that an immune response against HSV expressed in tumor cells was reported. Thus, there can be no anticipation of the present claims.

Claims 1-4, 9, 11 and 12 are not obvious over WO 95/29193
in view of Anderson et al. and Yewdell et al.

In rejecting claims 1-4, 9, 11 and 12 as obvious over WO 95/29193, in view of Anderson et al. and Yewdell et al., the Examiner fails to take into account the distinction between the claimed invention and WO 95/29193 as argued above in connection with the anticipation rejection. Anderson and Yewdell do not relate to this aspect of the claims, namely whether gp100 is non-immunogenic. Furthermore, nothing in the combination of references addresses the issues of whether the invention is obvious, namely whether it would be obvious that a therapeutically effective immune response to a non-immunogenic target could be obtained by administration of a heteroclitic peptide, or the characteristics of the response in terms of breaking tolerance. Thus, this rejection should be reversed.

Claims 1-4, 9 and 11 are not obvious over Lipford,
in view of Anderson et al. and Yewdell et al.

In rejecting claims 1-4, 9 and 11 as obvious over Lipford, in view of Anderson et al. and Yewdell et al., the Examiner fails to take into account the distinctions between the claimed invention and Lipford as argued above in connection with the anticipation rejection. Anderson and Yewdell do not relate to this aspect of the claims, namely whether an *in vitro* assay provides a teaching or suggestion of use an actual therapeutic for an antigen that is derived from an antigen with no immunogenic activity. In this regard, it is noted that Lipford says only that "the immune system favors certain epitopes, but **potential** targets for immune therapies **could probably** be subimmunogenic peptides." (Lipford, page 302, emphasis added). This is hardly a definitive statement and clearly leaves open whether Lipford, or the art in general could provide any reasonable expectation of success.

Claims 1, 2, 9 and 16 are not obvious over Huard et al.

Huard et al. has been discussed above in the context of the anticipation and the same differences that compel reversal of the anticipation rejection also render the claims not obvious. The CTL assays described are *in vitro* assays, and no *in vivo* results are shown. The lysed cells in

^{51}Cr assay are cells that have MHC-I binding sites (H-$2k^b$ or H-$2K^{bm8}$), not cells that express a target antigen. Furthermore, there is no suggestion that this is anything but a mechanistic study, and no reasons why a person skilled in the art would expect that the modified peptide would provide the benefits of being able to produce an *in vivo* immune response to an otherwise tolerated antigen. Thus, the claimed invention is not obvious over Huard et al.

Claims 1-4, 9 and 16 are not obvious over Huard et al
in view of Anderson et al. and Yewdell et al.

In rejecting claims 1-4, 9 and 16 as obvious over Huard, in view of Anderson et al. and Yewdell et al., the Examiner fails to take into account the distinctions between the claimed invention and Huard as argued above in connection with the anticipation and obviousness rejections. Anderson and Yewdell do not relate to this aspect of the claims, namely whether an *in vitro* assay provides a teaching or suggestion of use an actual therapeutic for an antigen that is derived from an antigen with no immunogenic activity. Thus, this rejection should be reversed for the same reasons as the rejection that does not include Anderson and Yewdell.

Respectfully submitted,

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Claims Appendix

1. A method for inducing a cellular immune response to a target peptide that is non-immunogenic in a mammalian subject and that is expressed by tumor cells of the mammalian subject, comprising administering to the mammalian subject an amount of a therapeutic antigen effective to induce a cellular immune response to the target peptide, wherein the therapeutic antigen comprises an immunogenic portion having an MHC-binding domain which binds to the major histocompatability complex (MHC) and an immune recognition domain which is recognized by T-cells, and wherein the therapeutic antigen is derived from the target peptide such that the MHC-binding portion binds to MHC with a greater affinity than the target peptide without material alteration of the immune-recognition portion, thereby inducing a therapeutically effective cellular immune response to the target peptide in the mammalian subject.

2. The method of claim 1, wherein the target peptide and the immunogenic portion of the therapeutic antigen each consist of from 8 to 14 amino acids.

3. The method of claim 1, wherein the therapeutic antigen further comprises a sorting signal for directing trafficking of the therapeutic antigen to the endoplasmic reticulum.

4. The method of claim 3, wherein the target peptide and the immunogenic portion of the therapeutic antigen each consist of from 8 to 14 amino acids.

9. The method of claim 1, wherein the MHC-binding domain binds to an MHC Class I molecule and the immune-recognition domain binds to a cytotoxic T cell.

11. The method of claim 1, wherein the target peptide binds to HLA-A* 0201.

12. The method of claim 1, wherein the target peptide is a self-peptide expressed in normal and tumor tissues of the mammalian subject.

13. The method of claim 12, wherein the target peptide derived from is gp75.

16. The method of claim 1, wherein the target peptide is a Herpes simplex glycoprotein B peptide and the therapeutic antigen is SSIEFARL (Seq. ID No. 10).

Evidence Appendix

none

Related Proceedings Appendix

none